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# COAGULATION HEMOSTASIS DISORDERS IN RHEUMATOID ARTHRITIS

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**Abstract.** A study was made of the features of hemostatic disorders in patients with rheumatoid arthritis, depending on the activity and duration of the pathological process. It has been shown that changes in the hemostasis system with a tendency to hypercoagulability and thrombosis are formed in patients with rheumatoid arthritis against the background of inflammation, depending on the activity of the pathological process and the duration of the disease. Persons with the debut of rheumatoid arthritis, not exceeding 18 months from the onset of the first clinical manifestations, in the absence of disease-modifying therapy, have laboratory manifestations corresponding to the activation of the hemocoagulation cascade. Inflammation in active articular syndrome at the onset is characterized by an increase in the adhesive properties of platelets, hypercoagulability, thrombinemia, and a decrease in the reserves of the fibrinolytic system. The most important prognostic laboratory sign associated with the severity of inflammation in rheumatoid arthritis is thrombinemia.

**Keywords:** rheumatoid arthritis, disease activity, disease duration, hemostasis.

**Introduction.** The hemostasis system maintains the vitality of the organism by controlling the effective blood supply to the organs. The imbalance of hemostatic reactions leads to the formation of blood loss, thrombosis, ischemia, and tissue necrosis [1]. The imbalance of various hemostasis systems is combined with an inflammatory response and has been studied in detail in infectious-septic conditions complicated by disseminated internal coagulation. Activation of hemostatic and inflammatory reactions is supported by pro-inflammatory mediators, among which TNF-α, IL-1β, IL-6, IL-17, and platelet-activating factor take the leading place [2, 3]. The formation of inflammation and activation of the hemocoagulation cascade, the severity of these reactions, are balanced by mediators with anti-inflammatory effects: IL-4, IL-10, IL-13, prostaglandin I2 [4].

Recent studies have shown the importance of hemostatic disorders in the course of chronic inflammatory diseases of a multifactorial nature without a clear evidence base for the participation of an infectious agent in the initiation of a pathological process. In rheumatoid arthritis (RA), activation of hemostasis can be catastrophic, causing cardiovascular mortality as the main reason for the decrease in life expectancy in RA patients. The subclinical course of hemostasis disorders is also considered, which promotes the proliferation of endothelial, smooth muscle, and immunocompetent cells of the vascular wall with the development of atherosclerosis [5–7]. The relationship between prothrombogenic changes in hemocoagulation and the progression of bone destruction, which is the basis of disabling changes in the joints, has been demonstrated [8].

Mutual participation in the mechanisms of realization of effects between hemostasis and inflammation is also indicated. Thus, circulating coagulation factors (thrombin, factor VIIa, factor Xa) have a pro-inflammatory potential, stimulating the synthesis of IL-6, IL-8, monocytic-chemotactic protein-1 [9]. Thrombin activates the expression of receptors on platelets and vascular endothelium, stimulating pro-inflammatory activity endothelial cells, fibroblasts, and synoviocytes [10].Physiological anticoagulants, components of fibrinolysis, in addition to participating in the main hemocoagulation processes, affect inflammation [11].The process of antithrombin citrullination with the participation of PADI4 is considered as a probable trigger mechanism for initiating the pathogenesis of RA [12].

This study was the result of a ten-year observation of patients with rheumatoid arthritis with an analysis of changes in hemostasis parameters at the onset, as the pathological process develops over time and in connection with its activity.

**Materials and methods of research**

The study included two groups of patients diagnosed with RA. The first group included 101 patients with newly verified very early and early RA (7.6 ± 3.9 months) who were followed up for 10 years, the second group included 363 patients with advanced and late RA (7.3 ± 6.4 years). ) [13] In the control group, the study of the hemostasis system and general clinical laboratory parameters was performed in 36 practically healthy individuals, comparable in sex and age with patients suffering from RA. The hemostasis system was studied at the stage of diagnosis, in the early and very early phases of RA before the start of the use of basic anti-inflammatory drugs (DMARDs), in dynamics after 5 and 10 years (group 1). In patients with advanced and late stages of the disease, with the ineffectiveness of previous therapy, the dose of the selected drug was adjusted (group 2). Patients in the debut were examined before the appointment of DMARDs. Subsequently, they were followed up at points 5 and 10 years from the onset of the disease and, like RA patients with a long history of the disease, they received methotrexate therapy at a dose of 10–17.5 mg per week, sulfasalazine 2 g per day, or combination therapy with these drugs.

Mathematical processing of the obtained results was carried out using the Statistica 6.0 software package. Comparison of variation series was carried out using Student's t-test and non-parametric Wilcoxon-Mann-Whitney U-test. Correlation analysis was carried out using Spearman's rank correlation method.

Informed consent was obtained from all patients.

**Results and discussion**

A group of patients of 101 patients with newly verified RA in the early and very early phase was followed up for 10 years with an intermediate observation point after 5 years. An analysis of inflammation indicators demonstrated a decrease in the laboratory activity of the disease in terms of erythrocyte sedimentation rate (ESR) ($p = 0.0005$) and the level of C-reactive protein (CRP) ($p = 0.022$) while taking DMARDs with an assessment after 5 years of follow-up. Subsequently, the level of

these indicators in the general group did not change significantly (p = 0.354 and p = 0.750, respectively).

There are data in the literature on an increase in the functional activity of platelets and excessive megakaryocytic production due to the progression of inflammation [16, 17]. As predictors of an unfavorable prognosis for the course of RA, the level of platelets in the peripheral blood is more than 300 × 109/l [18,19]. In the group of patients with early RA studied by us, platelet counts over 300 × 109/L were detected in 27.7% of cases. In all stages of observation determined by the design of the study, the level of platelets in the peripheral blood was detected in patients, significantly exceeding the results of the study of the control group. Thus, in patients with RA, there is an increase in the number of platelets in the blood compared to the control group, but the duration of the anamnesis does not significantly affect their content in the circulating blood. Next, we analyzed the change in the number of platelets in the peripheral blood depending on the activity of inflammation. Our data are consistent with the results of a study by Hundelshausen Ph. et al., who define the platelet as an immunocompetent cell with its own mechanisms of participation in the inflammatory process [19]: the increase in their blood levels in the present study increases in proportion to the activity of the pathological process in patients with RA.

Patients with RA had significant deviations from the control parameters in the coagulation, anticoagulation and fibrinolytic blood systems. An increase in the aggregation function of platelets, along with the activation of leukocytes and the formation of intercellular aggregates, was accompanied by a hypercoagulable shift according to the autocoagulation test. However, with the progression of the disease and the formation of predominantly proliferative changes in the tissues of the joints, there is an increase in the total antithrombin potential of the patient's blood (in terms of the thromboplastin and thrombin inactivation index), which corresponds to the stabilization of inflammation and an increase in the anticoagulant properties of the blood as a result of the effectiveness of the DMARD therapy. It should be noted that there are data in the literature on the presence of anti-inflammatory effects of anticoagulants used for treatment, including those of recombinant origin [20].

In patients with RA at an early stage of clinical manifestations, suppression of the internal mechanisms of fibrinolytic reactions was revealed, which is illustrated by a 6–8‑ fold lengthening of fibrin clot lysis. It can be assumed that the depression of the internal mechanism of fibrinolysis activation, revealed by this test, is associated with subclinical inflammation preceding the onset of the articular syndrome in RA and is observed further, regardless of the therapy, during ten years of observation of the study group of patients. This indicator of blood fibrinolytic activity was changed to varying degrees depending on the activity of RA. In particular, the minimum degree of RA activity, taking into account the DAS28 index (Disease Activity Score, assessment of 28 joints), was characterized by a moderate prolongation of

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XIIa- dependent lysis, and a high degree, by a significant depression of the studied indicator. Since the activation of fibrinolysis plays a significant role in the progression of cartilage destruction in RA [21], the depression of this system can be combined with a decrease in local inflammatory activity.

The final step in blood coagulation is known to be thrombin-induced transformation of fibrinogen into fibrin. Determination of the intermediate products of such a reaction - fibrin monomer and its complexes, referred to as soluble fibrin or soluble fibrin monomer complexes, is of great diagnostic value for recognizing the activation of blood coagulation. The detection of this marker in the examined patients showed a significant, compared with the control, increase in the content of soluble fibrin-monomer complexes in 93% of the examined patients (0.089 ± 0.010 g/l) already at an early stage of the pathological process. In the future, as RA progressed, this level remained stably high, illustrating high thrombogenic activity.

Next, we examined the dynamics of the above indicators, as well as leukocyte aggregation as the disease progressed. Regardless of the timing of the examination of patients and the start of DMARD therapy, permanent hypercoagulability was detected, which was detected in the autocoagulation test, with a progressive increase and strengthening of the antithrombin potential when assessing the thromboplastin and thrombin inactivation index. Thus, in particular, the inactivation index of thromboplastin and thrombin was 2.56 ± 0.07 versus 2.33 ± 0.08 ($p = 0.026$) in comparison with the early phase of RA and 2.00 ± 0.26 ($p = 0.008$) when compared with control. A decrease in the activity of one of the physiological anticoagulants, antithrombin III (at the onset, 108.03 ± 2.78, by the five-year duration of RA, 98.13 ± 2.63, $p = 0.012$) was noted within the range of normal values, but with a significant difference from control group ($p = 0.004$). The corresponding trend towards a decrease in the content of antithrombin III is traced with an increase in the activity of the pathological process in terms of the DAS28 level (from 102.2 ± 3.4% with minimal activity to 93.4 ± 2.6% with DAS28>5.1). Obviously, the increase in the thrombin inactivation index in our observations is a consequence of an increase in the antithrombin potential due to other physiological anticoagulants (protein C, protein S, thrombomodulin, TAF1, etc.).

Examination of patients in dynamics after 10 years showed a shift in the parameters of the hemolysate-aggregation test ($p = 0.016$) towards a decrease in platelet activity. This can be explained by the evolution of RA against the background of the use of DMARDs, antiplatelet therapy and be the result of their effective use [22].

As our observations have shown, hypercoagulability, detected by an autocoagulation test, persists in patients with an increase in the duration of the pathological process. Antithrombin activity in terms of the thromboplastin and thrombin inactivation index reaches the maximum difference with the control group ($p = 0.000$) in the dynamics of patient monitoring from the moment of RA formation

to the end of 10 years of illness. The activation of blood coagulation, documented by the level of soluble fibrin-monomer complexes, is most pronounced in the late phase of the disease, with no significant difference when comparing the results obtained with a 5- or 10-year history (0.096 ± 0.01 and 0.093 ± 0.01, respectively) .

In rheumatology, the level of fibrinogen is naturally regarded as a marker of the activity of the inflammatory process. In the present study, a decrease in the content of fibrinogen was recorded as a general response to the complex of therapy at the point of a 10-year follow-up. So, if at the onset it was 4.52 ± 0.14 g/l, then after 5 years of illness it was 4.12 ± 1.11 g/l (p = 0.039), and after 10 years it was 3.99 ± 0 .16 (p = 0.003), i.e., were close to the upper normal values.

**Conclusion.** Thus, in patients with rheumatoid arthritis, significant deviations in the coagulation, anticoagulation and fibrinolytic blood systems are revealed, the severity of which varies depending on the activity of the pathological process and the duration of the disease.

The revealed inhibition of XIIa-dependent fibrinolysis deficiency was associated with the severity of inflammation and was maximal at high clinical and laboratory activity of rheumatoid arthritis. It can be assumed that fibrinolysis depression develops as a result of current inflammation and has a protective function in terms of limiting the aggressive destruction of articular cartilage during rheumatoid inflammation.

A hypercoagulable shift was detected by us in patients with rheumatoid arthritis, regardless of the severity of inflammation and the duration of the disease history. At the same time, according to the results of the study, the antithrombin potential of the blood increases with the progression of the disease, which can be considered as a consequence of the anti-inflammatory effect of prolonged immunosuppressive therapy and a decrease in the exudative component in the evolution of the disease. The increase in antithrombin potential, according to our data, does not include the activation of antithrombin III, which requires a study to clarify the involvement of other natural anticoagulants in the formation of increased antithrombin activity in the blood of RA patients.

**References**

1. Shoikhet Ya.N., Momot A.P. On the role and relationship of hemostatic and inflammatory reactions in the formation of foci of purulent destruction of organs and tissues. Probl. wedge. honey. 2008. (4). 102–117.

2. Wallberg-Jonsson S., Cvetkovic J.T., Sundqvist K.G. et al. Activation of the immune system and inflammatory activity in relation to markers of atherothrombotic disease and atherosclerosis in rheumatoid arthritis // J. Rheumatol. 2002. 29. 875–882.

3. Firestein G.S, Budd R.C., Harris E.D. et al. Kelley's textbook of rheumatology. Philadelphia: W. b. Saunders Company, 2008. 2000 p.

4. Prete G.D., Carli M.D., Lammel R.M. et al. Th1 and Th2 T-helper cells exert opposite regulatory effects on procoagulant activity and tissue factor production by human monocytes // Blood. 1995. 86. 250–257.

5. Bijl M. Endothelial activation, endothelial dysfunction and premature atherosclerosis in systemic
autoimmune diseases // Neth. J. Med. 2003. 61. 273–277.

6. Schmitt-Sody M., Klose A., Gottschalk O. et al. Platelet-endothelial cell interactions in murine antigeninduced
arthritis // Rheumatology. 2005. 44. 885–889.

7. Nasonov E.L. Modern directions of immunological research in chronic inflammatory and autoimmune human diseases // Therapist. arch. 2001. 73. 43–46.

8. Nakashima T., Takayanagi H. The dynamic interplay between osteoclasts and the immune system // Arch .Biochem. Biophys. 2008. 473. 166–171.

9. Senden N.H., Jeunhomme T.M., Heemskerk J.W. et al. Factor Xa induces cytokine production and expression of adhesion molecules by human umbilical vein endothelial cells // J. Immunol. 1998. 161. 4318–4324.

10. Kitamoto Y., Nakamura E., Kudo S. et al. Thrombin in synovial fluid as a marker of synovial inflammation: a definite measurement by ELISA and correlation with VEGF // Clin. Chim. Acta. 2008. 398. 159–160.

11. Kuznik B.I. Physiology and pathology of the blood system. Chita, 2004. 336 p. Kuznik B.I. Physiology and pathology of the blood system. Chita, 2004. 336 p.

12. Chang X., Yamada R., Sawada T. et al. The inhibition of antitrombin by peptidylarginine deiminase 4 may contribute to pathogenesis of rheumatoid // Rheumatology. 2005. (44). 293–298.

13. Rheumatology: national guidelines / Ed. E.L. Nasonov, V.A. Nasonov. M.: GOETAR‑ Media, 2008. 720 p.

14. Steinbrocker O., Traeger C.N. Therapeutic criteria in rheumatoid arthritis // J. Am. Med. Assoc. 1949. 40. 659–662.

15. Barkagan Z.S., Momot A.P. Diagnosis and controlled therapy of hemostasis disorders. Moscow: Newdiamed, 2001. 296 p.

16. Naldini A., Aarden L., Pucci A. et al. Inhibition of interleukin-12 expression by α-thrombin in human peripheral blood mononuclear cells: a potential mechanism for modulating Th1/Th2 responses // Br. J. Pharmacol. 2003. 140. 980–986.

17. Endersen G.K. Evidence for activation of platelets in the synovial fluid from patients with rheumatoid arthritis // Rheumatol. Int. 1989. (9). 19–24.

18. Joseph J.E., Harrison P., Mackie I.J. et al. Increased circulating platelet‑ leukocyte complexes and platelet activation in patients with antiphospholipid syndrome, systemic lupus erithematosus and rheumatoid arthritis // Br. J. Haematol. 2001. 115. 451–459.

19. Hundelshausen Ph., Weber C. Platelets as immune cells // Circ. Res. 2007. 100. 27–40.

20. Varisco P.A., Peclat V., van Ness K. et al. Effect of thrombin inhibition on synovial inflammation in antigen induced arthritis //Ann. Rheum. Dis. 2000. 59. 781–787.

21. So A.K., Varisco P.A., Kemkes-Matthes B. et al. Arthritis is linked to local and systemic activation of coagulation and fibrinolysis pathways // J. Thromb. Haemost. 2003. (1). 2510–2515.

22. Farr M., Wainwright A., Salmon M. et al. Platelets in synovial fluid of patients with rheumatoid arthritis // Rheumatol. Int. 1984. 4. 13–17.